

18. (Amended)

As- The method of claim 17 wherein the bacteria are exposed to short sequential periods of stress by transferring the bacteria from growth media into non-nutritive media, then subsequently transferring the bacteria to non-nutritive media sequentially.

19. (Amended)

The method of claim 18 wherein the bacteria is exposed to three short sequential periods of stress.

REMARKS

I. DETAILED ACTION:

A. Priority

The Examiner has confirmed that the instant application is a continuation-in-part of Application No. 08/739,264 filed October 29, 1996 now U.S. Patent No. 5,840,318, which is a continuation-in-part of Application No. 08/517,016 filed October 18, 1995 now abandoned, which is a continuation-in-part of Application No. 08/376,175 filed January 20, 1994 now abandoned, which is a continuation-in-part of Application No. 08/059,745 filed May 11, 1993 now abandoned.

B. Election/Restriction

The Examiner has acknowledged Applicant's election of Group I **with traverse**. The Applicant's argument that Groups I-IV should be rejoined has been deemed to be non-persuasive. Applicants will cancel all other claims once the claimed invention is in condition for allowance.

## **II. CLAIM OBJECTIONS:**

Claim 12 was objected to by the Examiner for an informality in the claim. Examiner states that the abbreviation SRF "is used without defining its meaning when initially used". Applicants thank the Examiner for pointing out the informality. Applicants have amended claim 12 to specifically define the abbreviation SRF as "stress response factors". In light of the above, Applicants respectfully request that the objection to claim 12 be withdrawn.

## **III. CLAIM REJECTIONS - 35 U.S.C. 112, SECOND PARAGRAPH:**

Claims 1-19 stand rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 stands rejected as being vague and indefinite by the use of the phrase "filtering said separated product to remove any stress response products have a molecular weight greater than 10 kDa". The Examiner states that it is unclear whether the claimed filtering process is "removing only stress response products with a molecular weight greater than 10kDa or all substances with a molecular weight great than 10kDa".

In an effort to expedite prosecution, Applicants have now amended claim 1 to better clarify that the separated product being filtered may include substances in addition to stress response products. Applicants respectfully request withdrawal of the rejection to claim 1 under 35 U.S.C. 112, second paragraph.

Claim 8 stands rejected as the Examiner asserts that the use of the phrase "37°C or less" does not set forth a lower limit thus making it "impossible to determine at what temperature the claimed invention becomes nonfunctional". Claim 8 has now been amended to set a lower temperature limit. In addition, claim 9 has been cancelled.

Claim 10 stands rejected as being "vague and indefinite by the use of the term stationary phase". The Examiner states that it is "unclear whether Applicant is referring to a stage of replication or motility". Applicants respectfully traverse this rejection. It is clear to one skilled in the pertinent art that the term stationary phase in the claimed invention relates to the life cycle of the bacteria. As stated in the specification, the life cycle of bacteria consists of a lag phase, log phase, stationary phase, and the death phase (page 11, last paragraph). These phases are well known in the art. In addition, the nature of the present invention does not implicate that any claims should relate to the motility of the bacteria. However, in an effort to expedite prosecution, Applicants have amended claim 10 to clarify that the stationary phase is a replication phase within the life cycle of the bacteria, and as such, bring the claim into condition for allowance.

Claim 12 stands rejected for reciting the limitation "the method of claim 1 wherein the filtrate containing SRFs 10kDa...", as Examiner asserts there is insufficient antecedent basis for this limitation. Applicants thank the Examiner for pointing out this unintentional error and claim 12 has now been amended, thereby alleviating this objection.

Claims 17-19 stand rejected as the Examiner asserts that the "use of the term sequential periods of stress" is vague and indefinite. Applicants respectfully traverse this rejection. The specification clearly states that the short sequential periods of stress occur for "10-20 minutes" (page 12, first and second paragraph). In addition, the specification continues to discuss the method of performing sequential stress periods and the importance of shorter sequential stresses in order to yield more potent SRFs and SRFs of different potencies (page 12 of specification). However, in an effort to expedite prosecution,

w Applicants have amended claims 17-19 to better describe the sequential periods of stress described in the present application.

In light of the above amendments and remarks, Applicants assert that claims 1-19 are now in a condition for allowance. Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. 112, second paragraph.

**IV. DOUBLE PATENTING:**

Claims 1-19 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 5,840,318.

w Applicant is herein submitting a Terminal Disclaimer in compliance with 37 C.F.R. §1.321(c), which disclaims any term of a patent issuing from this application which would extend beyond the term of U.S. Patent No. 5,840,318. Therefore, Applicant submits that the claims are in proper form for allowance and respectfully requests reconsideration and withdrawal of the obviousness-type double patenting rejection.

**V. CLAIM REJECTIONS - 35 U.S.C. 103 over U.S. Patent 5,840,318:**

w Claims 1-19 stand rejected under 35 U.S.C. 103(a) as being obvious over U.S. Patent No. 5,840,318. Applicant respectfully submits a Terminal Disclaimer in compliance with 37 C.F.R. §1.321(c), rendering this rejection to these claims as moot. Applicant respectfully submits that U.S. Patent No. 5,840,318 does not make the claimed invention obvious.

**VI. CLAIM REJECTIONS - 35 U.S.C. 103 over De Vuyst et al.:**

m Claims 1-19 stand rejected under 35 U.S.C. § 103(a) as obvious over De Vuyst et al. Applicants respectfully traverse this rejection. Applicants strongly assert that the cited

reference does not teach, nor does it suggest, the claimed unique invention of the present application. Applicants respectfully request that this ground of rejection be withdrawn.

The differences between the De Vuyst bacteriocins and Applicant's stress response products was discussed at length in the prosecution of the 5,840,318 patent before the Examiner. Applicant submits the previous amendment and § 132 declaration detailing experiments which distinguish Applicant's SRF's and bacteriocins to perhaps refresh the Examiner's recollection. The pertinent part of the amendment is reproduced below:

De Vuyst teaches the production of a bacteriocin produced by *Lactobacillus amylovorus* DCE 471 which is bacteriocidal towards closely related *Lactobacillus* strains. (p. 818). De Vuyst further discloses that the bacteriocin-producing lactic acid bacteria could potentially be added to foods to stimulate bacteriocin production. (p. 825).

It is submitted that the Examiner is misinterpreting applicants invention which is not related to bacteriocins. Submitted herewith is a § 132 Declaration of Dr. Marshall which clearly establishes that the SRF compositions of the invention do not include bacteriocins or other compositions with bactericidal properties. The declaration details several experiments conducted using the methods of the invention and exposing the SRF compositions to *Lactobacillus helveticus*. The results show that the SRF compositions do not exhibit bactericidal activity. The results as depicted in Photograph 1 demonstrate that the preparations of the invention obtained from *L. monocytogenes*, *L. plantarum*, and *E. faecium* DO NOT inhibit growth of *Lactobacillus helveticus*. This is in stark contrast to the bacteriocin Nisin which is shown at the asterisk. Figure 2 shows that stressing *L. monocytogenes*, or even twice stressing *L. plantarum* and *E. faecium* or stressing heat killed *L. plantarum* and *E. faecium* do not result in bacteriocidal activity against *L. helveticus*. Figure 3 demonstrates that bacteriocins against *L. helveticus* are not produced by stressing *L. caseii*, *L. plantarum* or *E. faecium*, again no zones of inhibition are observed from the SRF's. Finally in Figure 4, 7 test strains (5 of *L. plantarum* and 2 of *E.*

*faecium*) were used both as SRF collecting strains and as test strains. Again, the bacteriocin Nisin inhibited all 7 strains while the SRF's collected from the same strains as well as from *L. casei* did not inhibit growth.

In contrast to the bacteriocin described in De Vuyst, the present invention claims the activation or modulation of the immune system of an animal through the administration of a product produced by bacteria subjected to stress which is then filtered. De Vuyst does not disclose the administration of a bacterial product to an animal which has been filtered from the bacteria, and it further does not teach that the product has been filtered to remove any molecules larger than 10 kDa.

**VII. CLAIM REJECTIONS - 35 U.S.C. 103(a) over De Vuyst et al. in combination with Nanji, or Perdigon or Emery:**

The remaining rejections comprise De Vuyst in combination with Nanji; (which discloses administration of lactic acid bacteria to animals for protection of endotoxin-mediated shock), Emery (which teaches the administration of a bacteriocin to create an immunogenic response); or Perdigon (which discloses lactic acid bacteria as adjuvants).<sup>1</sup> None of these alone or in combination teach or suggest the stress response factors of Applicant's invention which are distinct as shown in Applicant's § 132 declaration from bacteriocins. Applicant's invention relates to the unique discovery of SRF's which are neither suggested or taught by De Vuyst.

In light of the above remarks and the amended claims, Applicants strongly assert that neither the suggestion of the claimed unique invention nor the expectation of success is taught in the references cited by the Examiner. In fact, Applicants respectfully submit that any such suggestion would be merely hindsight application of the Applicants specification and claimed

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<sup>1</sup> Claims 1-15 and 17-19 were rejected over De Vuyst in view of Nanji, claims 16 was rejected over De Vuyst in view of Perdigon or Emery.

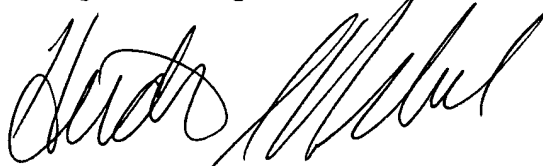
invention to the cited references. Applicants respectfully request reconsideration and withdrawal of the rejection to claims 1-19 under 35 U.S.C. 103(a).

**CONCLUSION**

In light of the above amendments and remarks, Applicants assert that the claims as amended are in condition for allowance. Applicants respectfully request reconsideration and withdrawal of the above rejections to claims 1-19.

It is not felt that any fee is due at this time, however if one is necessary, please charge Deposit Account No. 26-0084.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Heidi S. Nebel', written in a cursive style.

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